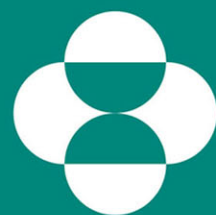


Getting e-Closer to Multi-Regional Clinical Trials



MERCK

INVENTING FOR LIFE

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Xiaohui Wang on Behalf of Lily Ling, Yuanyuan Dong and Yanhong Li
BARDS, MSD, China

Agenda

1. What's an MRCT?
2. Agency Requirements for Filings
3. The Planning and Design of Filings Based on MRCTs
4. Programming Strategy
5. Conclusion

1. What's an MRCT?



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- An MRCT¹ is a clinical trial conducted in more than one region under a single protocol. A region may refer to a geographical region, country or regulatory region.
 - MRCTs can facilitate simultaneous global development of a new drug and reduce some unnecessary duplication of studies conducted separately in different regions.
 - MRCTs can be the primary source of evidence for marketing application submissions in multiple regions.

¹ International conference on harmonization (ICH) E17

2. Agency Requirements for Filings



-
1. Sponsors need to understand the requirements of each agency and consider efficient processes for a new drug application (NDA).
 2. The overall principle for NDA in most countries is, first, the overall evaluation of the global clinical trial data, and then further trend analysis of the clinical trial data generated in subgroups.
 3. European Medicines Agency (EMA) requirements are usually less than FDA, while there are some additional requirements from Pharmaceuticals and Medical Devices Agency (PMDA) and Medical Products Administration (NMPA).

	FDA	EMA	PMDA	NMPA ^b
Annotated CRF (pdf)	√	√ ^a	√	√
SDTM/ADaM datasets (xpt)	√	√ ^a	√	√
cSDRG/ADRG (pdf)	√	√ ^a	√	
Define (PDF/XML)	√	√ ^a	√	√ ^c
Programs	√	√ ^a	√	
CSR	√	√	√	√
Subgroup CSR				√ ^d
Regular specific tables			JCTD ^e	CSS ^f

√: requested

^a: for EMA, the document is provided on request only.

^b: NMPA has issued draft version of application requirements for clinical trial database and related materials in electronic Common Technical Document (eCTD) for public comments³.

^c: It is called data description file.

^d: Only for China extension study.

^e: Japan subgroup analysis tables and side-by-side tables for Japan population and non-Japan population comparison included in the CTD module.

^f: China Specific Summary (CSS) is most likely required for NMPA submission if subgroup CSR is not available. The CSS includes some side-by-side tables and subgroup tables, provides a clinical overview of pharmacology, efficacy, and safety data to show the consistency between global study results and subgroup results.

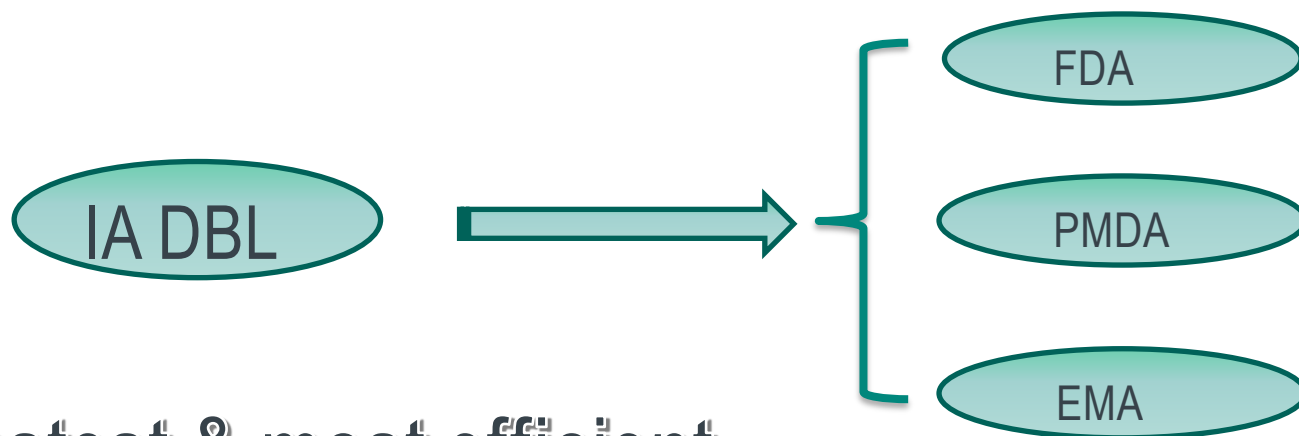
3. The Planning and Design of Filings Based on MRCTs



Case A: One DBL for Different Agency Submissions

There was a phase III randomized, open-label study to evaluate efficacy and safety of drug A in combination with treatment 1 versus treatment 2 monotherapy as a first-line treatment for locally advanced or metastatic renal cell carcinoma.

Challenge: Based on the first DBL data of interim analysis (IA), the package was submitted in US, EU and Japan simultaneously.



Fastest & most efficient

Submit filings parallelly using one data

Solution: A well-planned filing strategy, process and prompt action taken were quite critical factors to reach the target.

How?

a well-planned
filing strategy



prompt action taken



success

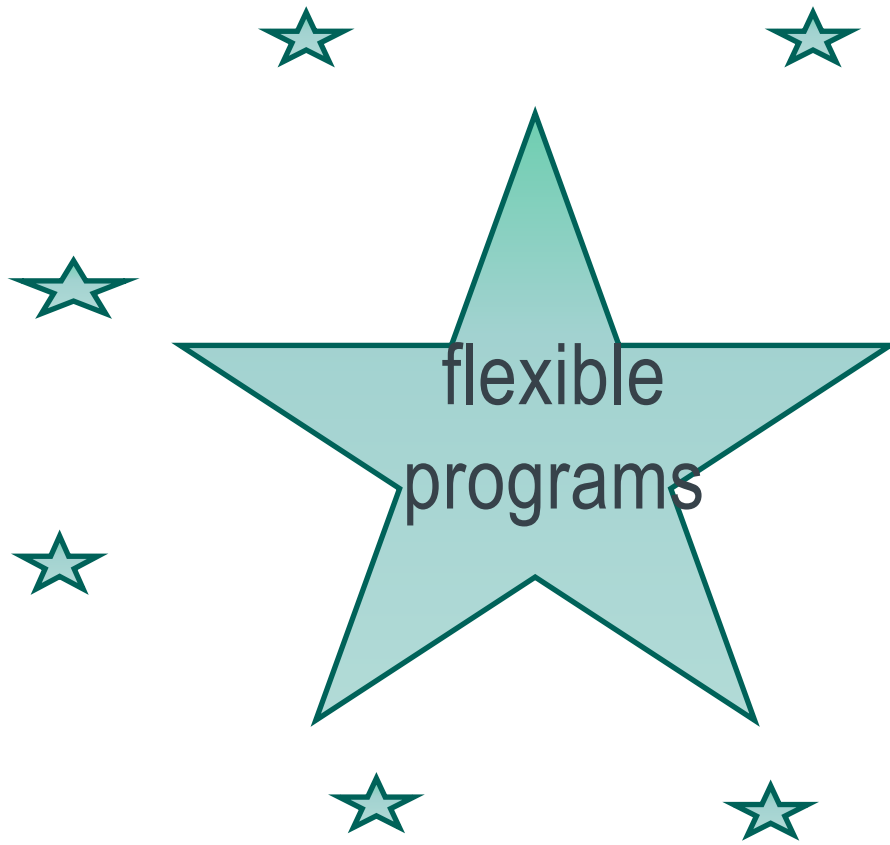
Case B: Global Trial without Specific Population

There was a randomized, double-blind, phase III study of chemotherapy with or without drug A in first Line metastatic non-squamous non-small cell lung cancer subjects.

Challenge: There was no Chinese population included.

Solution: Considering that the pooled Asian regional subgroup analysis results were consistent with the global results and there was an unmet medical need, the pooled Asian regional subgroup submission package was used to support the filing in China, received conditional approval by the regulatory authority.

How to make quick delivery with high quality for unexpected filing?

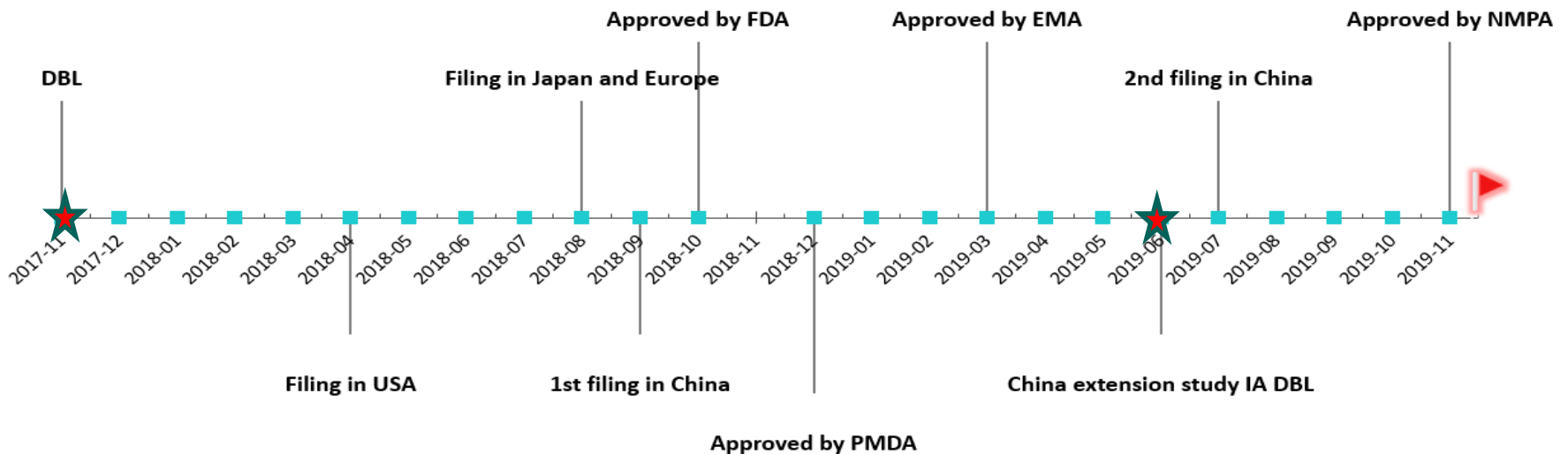


Case C: Different DBLs for Different Agency Submissions

There was a randomized, double-blind, phase III study chemotherapy with or without drug A in first line metastatic squamous non-small cell lung cancer subjects.

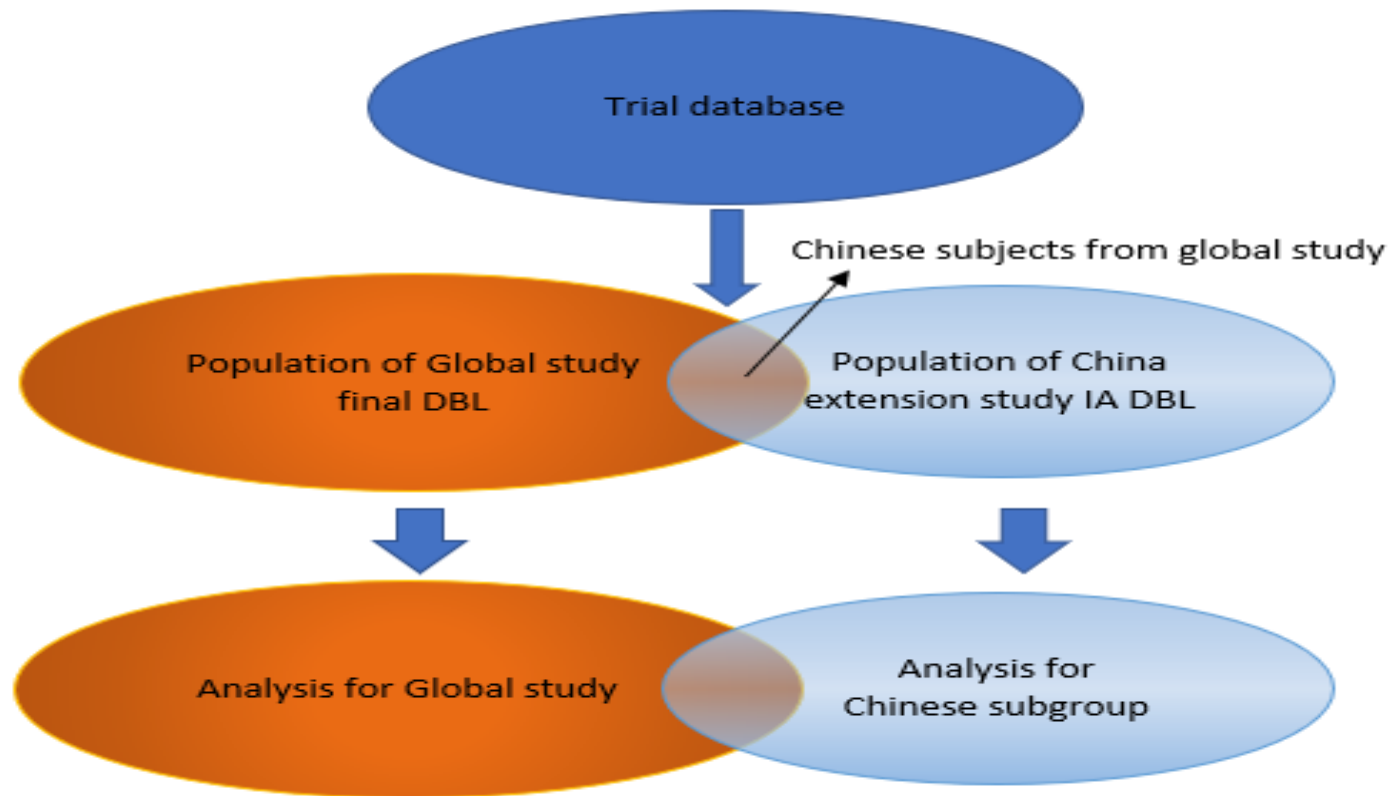
Challenge: Chinese population was too small.

Solution: The extension study was designed in China.



How to complete the work quickly and with high quality?

The Process Chart for Different DBLs



4. Programming Strategy



Purpose	Function	Programming Code Examples
To select different population automatically in the TFL programs	Define the population selection criteria and corresponding subtitle	<pre> %let pop_trt=%str(TRTFL='Y'); *** global group population** %let subtitle_trt=%str((TRT Population)); *** global group subtitle** %let pop_trt=%str(TRTFL='Y' and country='CHN'); *** subgroup population** %let subtitle_trt=%str((China TRT Population)); *** subgroup subtitle** </pre>
To differentiate file names for different population results	Adjust the output file names with suffix according to different submission needs	<pre> %let sub_output_nam = ; ***the global group output file name will be study0pop** %let sub_output_nam = %str(0chn); ***the subgroup output file name will be study0pop0chn** </pre>

Purpose	Function	Programming Code Examples
Adjust the file path to save the TLFs or datasets for different population results	Define the file path with different folder names	<pre>%let sub_pop_path = %str(\china); ***folder path**;</pre> <pre>%let sub_pop_path %str(\east_asia); ***folder path**;</pre> <pre>libname outdata "<Path1>\outdata\&sub_pop_path."; ***the libname of output datasets based on different region**;</pre>

Folder Name	Folder level	Content Description
Study path	1	Study path for global level or region level at one milestone
outtable	2	Study table folder for global level or region level
region1	3	Subgroup 1 table folder only for region level, e.g. China, East-Asia
region2	3	Subgroup 2 table folder only for region level, e.g. China, East-Asia
outdata	2	Subgroup output datasets folder for global level or region level
region1	3	Subgroup 1 output datasets folder only for region level, e.g. China, East-Asia
region2	3	Subgroup 2 output datasets folder only for region level, e.g. China, East-Asia
...		

Purpose	Function	Programming Code Examples
To adjust the stratification factors for different analysis methods (stratified / unstratified) according to different population needs	The stratification factors selection	<pre> ***Stratified variables and stratification factors in the footnote **; %let strata=var1; %let stra_footnote=%str(Based on analysis method stratified by variable 1); ***Unstratified variables and unstratified information in the footnote **; %let strata=; %let stra_footnote=%str(Based on analysis method unstratified); ***(un)stratified analysis selection based on the analysis needs** ; %macro strata; proc sql print; create table adsl as select usubjid %if "&strata" ne "" %then %do; , &strata. as stratum %end; %else %do; , 1 as stratum %end; from lptda.adsl; quit; %mend; </pre>

5. Conclusion



MRCTs play an important role in the global drug development.

It is a good practice to plan all the submissions based on MRCTs ahead of time.

Submission team in different regions should work together during the planning phase to make sure the consistency of the TFLs for similar analysis to achieve maximum efficiency.

In the future, it would be more standardized for eCDT requirements from different authorities.

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- Xiaohui Wang

Contact information

Author	Mail
Lily Ling	li.li.ling@merck.com
Yuanyuan Dong	yuan.yuan.dong@merck
Yanhong Li	yanhong.li1@merck

THANK YOU



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